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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/810,793	03/26/2004	Zhijian J. Chen	MPI96-031CP1DV1CPACN2M	1019
30405	7590	02/12/2007	EXAMINER	
MILLENNIUM PHARMACEUTICALS, INC. 40 Landsdowne Street CAMBRIDGE, MA 02139			OUSPENSKI, ILIA I	
		ART UNIT	PAPER NUMBER	
		1644		
SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE		DELIVERY MODE	
3 MONTHS	02/12/2007		PAPER	

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)
	10/810,793	CHEN, ZHIJIAN J.
	Examiner	Art Unit
	ILIA OUSPENSKI	1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 07 November 2006.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 7,8 and 10-19 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 7,8 and 10-19 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. The examiner of this application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to ILIA OUSPENSKI, Group Art Unit 1644, Technology Center 1600.
2. Applicant's amendment/remarks, filed on 11/07/2006, are acknowledged.

Claims 7 – 8 and 10 – 19 are pending.

This Office Action will be in response to applicant's amendment and arguments, filed on 11/07/2006.

The rejections of record can be found in the previous Office Action, mailed on 05/12/2006.

3. The rejections of record have been withdrawn in view of Applicant's amendment and arguments.

It is noted that New Grounds of Rejection are set forth herein.

4. The disclosure is objected for failing to comply with 37 CFR 1.821(d), because the sequences disclosed at least on page 85, lines 14 – 16, are not accompanied by SEQ ID Numbers.

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5. The use of trademarks has been noted in this application (e.g. SEPHADEX™ on page 94, line 9). Each letter of the trademarks should be capitalized wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks. See MPEP 608.01(v). Applicant is requested to review the application for any additional instances of trademark use and make appropriate corrections.

6. Claim 10 is objected to because of redundant recitations of "antigen-binding fragment." Applicant is invited to amend the claim to recite "The antibody or antigen-binding fragment thereof of claim 7, wherein said antigen-binding fragment is selected from the group consisting of an F(ab')₂ fragment, and Fab' fragment, an Fab fragment and an Fv fragment."

7. The following is a quotation of the **first paragraph of 35 U.S.C. 112:**

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 18 and 19 are rejected under **35 U.S.C. 112, first paragraph**, because the specification, while being enabling for a diagnostic kit comprising a conjugate comprising a ubiquitin dependent kinase or subunit thereof, wherein said kinase phosphorylates IκBα (SEQ ID NO:9) at serine residues 32 and 36, the kinase being a complex of approximately 700 kDa molecular weight as determined by gel filtration chromatography or size exclusion chromatography,

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does not reasonably provide enablement for a diagnostic kit comprising a conjugate comprising a generically recited "binding partner" of the recited antibody. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not enable one of skill in the art to make and use the invention as claimed without undue experimentation. Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized in In re Wands (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, limited working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

The specification discloses only a single type of "binding partner" of the recited antibody, namely, a ubiquitin dependent kinase or subunit thereof, wherein said kinase phosphorylates I κ B α (SEQ ID NO:9) at serine residues 32 and 36, the kinase being a complex of approximately 700 kDa molecular weight as determined by gel filtration chromatography or size exclusion chromatography (Examples 3 – 7 at pages 96 – 99). The instant generic recitation encompasses in its breadth various other types of "binding partners," such as, for example, a secondary antibody, an Fc receptor, or other antibody-binding agents such as protein A.

A person of skill in the art is not enabled to make and use any "binding partner" commensurate with the scope of the claims as presently recited, because it was well known in the art at the time the invention was made that molecules having highly diverse structural and biochemical properties can function as "binding partners" to proteins, including antibodies. Huang (Pharmacology and Therapeutics, 2000, 86: 201 – 215; see entire document) reviews e.g. on page 202 the daunting task faced by the

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skilled artisan in developing molecules which would bind to a specific target, and notes that the process requires long periods of trial and error testing. The structure of such molecules cannot be readily determined by one of skill in the art based upon the guidance provided in the specification as-filed. Therefore, Applicant does not provide a sufficiently enabling disclosure regarding how to make and use "binding partners" of the recited antibody, other than a ubiquitin dependent kinase or subunit thereof, wherein said kinase phosphorylates I κ B α (SEQ ID NO:9) at serine residues 32 and 36, the kinase being a complex of approximately 700 kDa molecular weight as determined by gel filtration chromatography or size exclusion chromatography, to which the recited antibody specifically binds.

The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 18 24 (CCPA 1970). "It is not sufficient to define the recombinant molecule by its principal biological activity, e.g. having protein A activity, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property." Colbert v. Lofdahl, 21 USPQ2d, 1068, 1071 (BPAI 1992).

In view of the quantity of experimentation necessary, the unpredictability of the art, the lack of sufficient guidance in the specification, the limited working examples, and the limited amount of direction provided given the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

9. Claims 7 – 8 and 10 – 19 are rejected under **35 U.S.C. 112, first paragraph**, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

Applicant is not in possession of an antibody or an antigen-binding fragment thereof which binds specifically to a generically recited "a kinase or a subunit thereof," wherein the kinase is defined solely by its ability to phosphorylate I_KB α and by approximate molecular weight.

Applicant has described a species of kinase within the broadly recited genus, specifically a ubiquitin dependent kinase with the recited properties (Examples 3 – 7 at pages 96 – 99). Therefore, Applicant is only in possession of an antibody or antigen-binding fragment thereof which binds specifically to a ubiquitin dependent kinase or subunit thereof, wherein said kinase phosphorylates I_KB α (SEQ ID NO:9) at serine residues 32 and 36, the kinase being a complex of approximately 700 kDa molecular weight as determined by gel filtration chromatography or size exclusion chromatography.

One of skill in the art at the time the invention was made was aware that many different kinases can phosphorylate I_KB α , such as, for example, cAMP-dependent protein kinase (PKA) and protein kinase C (PKC) (Diaz-Meco et al., of record – Ref. B10 on IDS filed on 03/25/2004; see entire document, in particular, e.g. the Abstract), casein kinase II (CKII) (Barroga et al.; of record – Ref. A8 on IDS filed on 03/25/2004; see entire document, in particular, e.g. the Abstract), dsRNA-activated p68 protein kinase (PKR) (Kumar et al.; of record – Ref. C9 on IDS filed on 03/25/2004; see entire document, in particular, e.g. the Abstract), and other kinases (Kuno et al.; of record – Ref. C10 on IDS filed on 03/25/2004; see entire document, in particular, e.g. the Abstract).

Furthermore, there is an extensive structural variability among these families of kinases and even within the families. For example, Hoffman (FASEB J., 1997, 11: 649 – 669) reviews the structural and functional variability within the family of C kinases (see

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entire document, in particular, e.g. pages 652 – 653 and 559, and Tables 2, 3, and 6). Hoffman notes that this extensive structural variability, in particular within the phosphoryl transfer region, the pseudosubstrate domain, and others, precludes a ready prediction of functional properties, such as substrate specificity or inhibitor profile (see e.g. Perspectives at pages 660 – 662).

Given the large number of kinases which phosphorylate I κ B α , the extensive structural variability between these kinases, the limited identifying characteristics of the recited kinase, solely its ability to phosphorylate I κ B α and approximate molecular weight, are insufficient to convey with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention. In the absence of sufficient structural characteristics that are shared by members of the genus of "kinase," one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. See University of California v. Eli Lilly and Co. 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997).

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, §1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species; then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3).

The written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ... i.e.,

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complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Guidelines, 66 Fed. Reg. at 1106.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

10. The following is a quotation of the appropriate paragraphs of **35 U.S.C. 102** that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 7 – 8, 10 – 11, and 13 – 17 are rejected under **35 U.S.C. 102(b)** as being anticipated by Yoshitaka et al. (US Patent No. 5,219,748; 06/15/1993), as

evidenced by Diaz-Meco et al. (of record – Ref. B10 on IDS filed on 03/25/2004) and by Pracht et al. (Cellular Signaling, 2006, doi:10.1016/j.cellsig.2006.07.023).

Yoshitaka et al. teach antibodies to human and rat protein kinase C (see entire document, in particular, e.g. column 1 lines 55 – 60, column 4 lines 14 – 19, column 9 lines 7 – 13, and column 16, lines 52 – 59). Also taught is an antibody to kinase C which is detectably labeled with a radioisotope, specifically with ¹²⁵I protein A (e.g. column 16 lines 45 – 65), and ant-kinase C antibody immobilized on nitrocellulose filters, i.e. a solid support (e.g. column 16 lines 45 – 65).

Yoshitaka et al. also teach a method of detecting protein kinase C in a sample using the antibody to kinase C, comprising contacting the sample with the antibody under conditions such that an immunocomplex forms, and detecting the presence of the antibody bound to the kinase (e.g. column 16 lines 45 – 65).

Diaz-Meco et al. provide evidence that protein kinase C phosphorylates I_KB α (see entire document, in particular, e.g. the Abstract, and Results at pages 2842 – 2843).

Pracht et al. provide evidence that protein kinase C associates with the B cell antigen receptor complexes, both IgD and IgM-containing, i.e. it is a part of a complex of approximately 700 kDa (see entire document, in particular, e.g. Results at pages 3 – 4, and Figure 1).

Since the kinase taught by Yoshitaka et al. and the recited kinase have the ability to phosphorylate the same substrate and are present in a complex of about the same molecular weight, they are presumed to have the same specificity for serine residues 32 and 36 of I_KB α . The Office is not in a position to test the kinase described in the prior art for the functional properties recited in the instant claims. The burden is on the

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applicant to establish a patentable distinction between the claimed and referenced antibodies. See In re Best, 195 USPQ 430, 433 (CCPA 1977); In re Marosi, 218 USPQ 289, 292-293 (Fed. Cir. 1983); and In re Fitzgerald et al., 205 USPQ 594 (CCPA 1980).

Therefore, the antibody of Yoshitaka et al., in view of its inherent properties, as evidenced by Diaz-Meco et al. and by Pracht et al., anticipates the instant claims. Claim 8 is anticipated, because an antibody which binds to a complex, inherently binds to a subunit of said complex.

12. The following is a quotation of **35 U.S.C. 103(a)** which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 7 and 10 are rejected under **35 U.S.C. 103(a)** as being unpatentable over Yoshitaka et al. (US Patent No. 5,219,748) (as evidenced by Diaz-Meco et al. (of record) and by Pracht et al. (cited above)), in view of Kuus-Reichel et al. (Clin. Diagn. Lab. Immunol., 1994, 1: 365 – 372).

Yoshitaka et al. have been discussed supra, and teach antibodies to a kinase which is encompassed by the scope of the instant recitation, as evidenced by Diaz-Meco et al. and by Pracht et al. Yoshitaka et al. envisioned the use of anti-kinase antibodies for therapy, as evident at column 9, lines 8 – 20.

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Yoshitaka et al. do not specifically exemplify antigen-binding fragments of anti-kinase C antibodies.

Kuus-Reichel et al. teach that antibody fragments, such as Fab and Fv, can be readily obtained by techniques routine in the art, and are less immunogenic than intact antibodies and therefore are more useful for treatment of disease (see entire document, in particular, e.g. page 365, second column, second full paragraph; and Summary at pages 369 – 370).

Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to produce antigen-binding fragments, such as Fab and Fv, as taught by Kuus-Reichel et al., of anti-kinase C antibodies taught by Yoshitaka et al.

One of ordinary skill in the art would have been motivated to do so, because of well-appreciated advantages of such fragments, e.g. for therapy, as taught by Kuus-Reichel et al., in view of the teachings of Yoshitaka et al. that anti-kinase C antibodies can be used for therapy.

Furthermore, one of ordinary skill in the art at the time the invention was made would have a reasonable expectation of success in producing Fab or Fv fragments of anti-kinase C antibodies, because production of antigen-binding fragments of antibodies was routine in the art at the time the invention was made, as evidenced by Kuus-Reichel et al.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

14. Claims 7, 11, and 12 are rejected under **35 U.S.C. 103(a)** as being unpatentable over Yoshitaka et al. (US Patent No. 5,219,748) (as evidenced by Diaz-Meco et al. (of record) and by Pracht et al. (cited above)), in view of Campbell (General properties and applications of monoclonal antibodies, Elsevier Science Publishers, 1984, pages 2 - 32).

Yoshitaka et al. have been discussed supra, and teach antibodies to a kinase which is encompassed by the scope of the instant recitation, as evidenced by Diaz-Meco et al. and by Pracht et al. Yoshitaka et al. envisioned the use of anti-kinase antibodies for therapeutic and diagnostic applications (e.g. column 9, lines 8 – 20).

Yoshitaka et al. do not specifically exemplify monoclonal anti-kinase antibodies; or hybridomas which produce such antibodies.

Campbell reviews that methods of production of monoclonal antibodies were routine in the art, and that monoclonal antibodies have numerous advantages over polyclonal antibodies, including those critical in therapeutic and diagnostic applications (see entire document, in particular, e.g. section 1.2.1 at pages 5 – 7). Campbell also teach that monoclonal antibodies are routinely produced by hybridoma cells (e.g. pages 2 – 4).

Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to produce monoclonal antibodies, as taught by Campbell, to the kinase taught by Yoshitaka et al.

One of ordinary skill in the art would have been motivated to do so, because of well-appreciated advantages of monoclonal antibodies for therapeutic and diagnostic uses, as reviewed e.g. by Campbell, and the teachings of Yoshitaka et al. regarding therapeutic and diagnostic uses of anti-kinase C antibodies.

One of ordinary skill in the art at the time the invention was made would have a reasonable expectation of success, because production of monoclonal antibodies was routine in the art at the time the invention was made, as taught by Campbell.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

15. Claims 18 and 19 are rejected under **35 U.S.C. 103(a)** as being unpatentable over Yoshitaka et al. (US Patent No. 5,219,748) (as evidenced by Diaz-Meco et al. (of record) and by Pracht et al. (cited above)), in view of Zuk et al (U.S. Patent No. 4,281,061; 06/28/1981).

Yoshitaka et al. have been discussed supra, and teach antibodies to a kinase which is encompassed by the scope of the instant recitation, as evidenced by Diaz-Meco et al. and by Pracht et al. Yoshitaka et al. envisioned the use of anti-kinase antibodies for diagnostic applications (e.g. column 9, lines 8 – 20), and teach a method of detection of the kinase using an antibody to the kinase, a conjugate comprising a binding partner of the antibody and a label - ¹²⁵I protein A, which also serves as a detection reagent (e.g. column 16 lines 45 – 65), and a wash reagent (*ibid*).

Yoshitaka et al. do not specifically exemplify a kit comprising container means comprising the anti-kinase C antibody, and a second container means comprising a binding partner and a label, or a wash reagent or detection reagent.

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Zuk et al. teach that reagents for an immunoassay can be provided as kits as a matter of convenience and to optimize the sensitivity of the assay in the range of interest (column 22, line 62 – column 23, line 4).

Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to place the immunoassay reagents taught by Yoshitaka et al. into a kit format as taught by Zuk.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, because of the art-appreciated advantages and convenience of kits, as taught by Zuk, and have a reasonable expectation of success, because it was well within the skill of the art at the time the invention was made to place reagents into containers.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

16. Conclusion: no claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILIA OUSPENSKI whose telephone number is 571-272-2920. The examiner can normally be reached on Monday-Friday 9 - 5.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



ILIA OUSPENSKI, Ph.D.

Patent Examiner

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CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
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February 5, 2007



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